

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

LIVSHITS et al.

Application No.: 09/466,935

Filing Date: December 20, 1999

For: NOVEL GENE AND METHOD FOR
PRODUCING L-AMINO ACIDS

Art Unit: 1656

Examiner: David J. STEADMAN

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Confirmation No.: 1750

BRIEF FOR APPELLANT

Mail Stop Appeal Brief - Patents

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

Sir:

COMES NOW the Appellant to present this Brief in support of the appeal of the rejection of Claims 77-84 in the above-captioned patent application. The Notice of Appeal was timely filed on 17 September 2008. Although these claims are not finally rejected, they have been twice rejected. As this Appeal Brief is filed on or before November 17, 2008, this Brief is timely filed.

It is not believed that extensions of time are required, beyond those that may otherwise be provided for in accompanying documents. If, however, additional extensions of time are necessary to prevent abandonment of this application or dismissal of this appeal, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and the Commissioner is hereby authorized to charge fees necessitated by this paper, and to credit all refunds and overpayments, to the credit card authorized on the attached PTO-2038.

For the following reasons, Appellant respectfully submits that the rejection of each of Claims 77-84 in this application is in error, and therefore respectfully requests reversal of the rejections.

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I. Real Party in Interest

The real party in interest is Ajinomoto Co., Inc, a corporation of Japan.

II. Related Appeals and Interferences

The child application, 11/106455 ("the '455 application") is also currently on appeal, as the Appeal Brief in that case is being filed on the same day as the instant Appeal Brief. Currently, the claims of the instant application are terminally disclaimed over the claims of the '455 application.

III. Status of Claims

Claims 1-76 are cancelled. Claims 77-84 are pending and appealed. No claims are in condition for allowance. Claims 77-84 stand rejected in the Office Action dated 22 July 2008, and are on appeal.

IV. Status of Amendments

All amendments to the claims have been entered.

V. Summary of Claimed Subject Matter

Claim 77: A method of producing an L-amino acid comprising A) cultivating in a culture medium a bacterium transformed with a DNA that encodes a protein comprising the amino acid sequence of SEQ ID NO: 4, B) removing solids including cells from the medium; and C) purifying said L-amino acid from the medium obtained in step B), wherein said L-amino acid is present in the medium obtained from step B) in a larger amount than that produced if the bacterium of step A) was not transformed with said DNA.. (see specification, page 8, lines 6-12, page 14, line 15 - page 16, line 8, page 21, line 8 -- page 23, line 7).

VI. Grounds of Rejection to Be Reviewed on Appeal

A. Whether Claims 77-84 are unpatentable under 35 U.S.C. § 103(a) over Kobayashi

et al. in view of Kaplan *et al.*, Georgiou *et al.*, and Begot *et al.*, as evidenced by Zakataeva *et al.* and Kruse *et al.*.

VII. Argument

A. Legal Standard – 35 U.S.C. §103

Claimed subject matter is obvious in light of the prior art if it would have been obvious to one of ordinary skill in the relevant art at the time the invention was made. 35 U.S.C. § 103(a). In considering the entire prior art in the relevant field, the claimed subject matter is obvious if the prior art “would have suggested to one of ordinary skill in the art that this [invention should be made] and would have a reasonable likelihood of success.” *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

Obviousness can be shown either directly by demonstrating the technical motivation to combine the prior art, *Life Technologies, Inc. v. Clontech Laboratories, Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000), by showing that there existed at the time of the invention a known problem for which there was an obvious solution, *KSR International Co. v. Teleflex Inc. et al.*, No. 04-1350, slip op. at 16 (S.Ct., April 30, 2007), or indirectly through “secondary considerations” after the claimed subject matter was invented, *Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*, 807 F.2d 955, 960 (Fed. Cir. 1986). However, neither the patentee’s particular motivation for making the invention, nor their avowed purpose, controls. *KSR*, slip op. at 17. To show a motivation to combine prior art, it is not enough to simply identify different references that might be combined in hindsight; showing obviousness may be accomplished by showing a motivation to combine the pieces (*Velander v. Garner*, 348 F.3d 1359, 1363 (Fed. Cir. 2003)) or showing a combination of familiar elements according to known methods which yields no more than predictable results. *KSR*, slip op. at 12. That motivation or reason might come from a reference or from the knowledge of an artisan of ordinary skill. The level of ordinary skill in an art is based on a number of factors, including the educational level of the inventor, the type of problems encountered in the art, prior solutions to those problems, and

the speed of innovation in the art. *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 666-67 (Fed. Cir. 2000).

The U.S. Supreme Court has very recently addressed the obviousness of a combination of known elements. Although a rigid application of the Court of Appeals for the Federal Circuit's "teaching, suggestion, or motivation" test was rejected, the Court stated that "a combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR, slip op.* at 12. For example, the Court explained, when the prior art elements work together in an unexpected and fruitful manner, a finding of non-obviousness is supported. *Id.* (citing *United States v. Adams*, 383 U.S. 39, 40 (1966)). If, however, the combination of old elements does no more than they would in separate, sequential operation, even though the combination might perform a useful function, the combination is likely non-obvious. *Id.* at 13 (citing *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57 (1969)). Finally, the Court stated that "[i]f a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability." *Id.* (citing *Sakraida v. AG Pro, Inc.*, 425 U.S. 273 (1976)).

"Secondary considerations" focus on how the invention was received in the market; a very successful or surprising invention is probably not obvious. *See Custom Accessories, Inc.*, 807 F.2d at 960. The "secondary considerations" considered by the courts include: commercial success, copying of the invention by others, licensing of the invention, evidence of a long-felt need for the invention, skepticism by skilled artisans that the claimed invention could be achieved, prior failures of others to achieve the same result, and unexpected results. *Id.*; *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 316 (Fed. Cir. 1985). No secondary consideration is required for an invention to be non-obvious, but a court may use evidence of secondary considerations in its determination of obviousness (or non-obviousness). *Custom Accessories, Inc.*, 807 F.2d at 960.

B. The rejection of Claims 77-84 under 35 U.S.C. § 103(a) is in error

Claims 77-84 were rejected under 35 U.S.C. § 103(a), as reciting subject matters that

allegedly are unpatentable over Kobayashi *et al.* (hereinafter, "Kobayashi"), in view of Kaplan *et al.* (hereinafter "Kaplan"), Georgiou *et al.* (hereinafter "Georgiou"), and Begot *et al.* (hereinafter "Begot"), as evidenced by Zakataeva *et al.* (hereinafter, "Zakataeva") and Kruse *et al.* (hereinafter, "Kruse"). Appellant respectfully requests reconsideration of this rejection.

The claims are drawn to a method of producing an L-amino acid by 3 distinct, manipulative steps. That is, step 1 is cultivating the bacterium, step 2 is removing solids including cells from the medium, and step 3 is purifying the L-amino acid from the medium obtained in step 2. These are distinct steps as indicated in the claim, for example, that the L-amino acid is purified from the medium obtained in the second step. Clearly, one cannot purify the L-amino acid recited in step 3 without first obtaining the medium in step 2, that is, a medium having the solids, including cells, removed. Finally, the claims recite that the produced amino acid is present in the medium obtained from step B) in a larger amount than that produced if the bacterium of step A) was not transformed with said DNA.

Simply stated, the references either singly or in combination do not teach or suggest a method of producing an L-amino acid using a bacterium which has been transformed with a DNA encoding a protein having the amino acid sequence of SEQ ID NO: 4 by the specifically claimed steps, and especially that a larger amount of the L-amino acid is produced than when the bacteria is not transformed with the DNA.

Kobayashi is cited for teaching an *E. coli* host cell transformed with vector pAB104, which comprises a DNA segment which includes the region between and including genes *pldA* and *pldB* (see p. 1012, figure 4 and p. 1014, figure 6). This region includes the DNA of SEQ ID NO: 3, which encodes the amino acid sequence of SEQ ID NO: 4, as demonstrated by Zakataeva. Appellants have agreed with this interpretation of these references. Kobayashi does not teach any method steps for producing an amino acid, and specifically does not teach steps B) and C) of the claimed method. Specifically, Kobayashi does not teach production of an L-amino acid in a large amount, and particularly that transforming the bacteria with the DNA which encodes the protein of SEQ ID NO: 4 will result in a larger amount of L-amino acid than when the bacteria is NOT transformed with said DNA.

The Examiner has asserted that Kobayashi teaches that on page 1009 in the section entitled “Enzyme Assay” at the bottom of column 1, the strain harboring the desired vector is cultured, and then the cells are ‘spun down’ and washed. The pellet, which contains the solids such as the cells and cellular debris, was further processed and the objective enzymes were further purified from the processed pellet. The medium is not used for any purpose and is likely discarded, as it is NOT further processed. There is no disclosure of recovering any substance from the medium or supernatant that remains after the ‘spinning’. There is no disclosure that any substance *could be* isolated from the medium or supernatant. More importantly, the reference of Kobayashi fails to teach, either explicitly or implicitly, step C of claim 1, that is, the purification of the L-amino acid from the medium obtained in step B in amounts larger than if the bacteria had not been transformed with the DNA encoding an amino acid sequence of SEQ ID NO: 4.

The Examiner has stated that “by practicing the method of Kobayashi, one of ordinary skill in the art would be “removing solids” in accordance with step B and purifying said L-amino acid” in accordance with step C simultaneously.” (see page 3 of the Office Action mailed April 16, 2007 and continued assertion of this position in the Office Action mailed July 22, 2008 on pages 9-10). The Examiner explains that the step of centrifuging the cells would simultaneously remove solids from the medium and purify the L-amino acid, which is in the cells, from the medium. This interpretation of the prior art and application to the claims is a clear error. This is because the claims distinctly recite 3 manipulative steps, that is, cultivating the bacterium, removing solids including cells from the medium, and purifying the L-amino acid *from the medium* obtained in the second step. These are distinct steps as indicated in the claim, for example, that the L-amino acid is purified from the medium obtained in the second step. Clearly, one cannot purify the L-amino acid without first obtaining the medium in the second step, that is, a medium having the solids, including cells, removed. The Examiner has erred in interpreting that steps B and C can be combined into one. It is clear that step C cannot be conducted without first obtaining the medium from step B. It is impossible to combine them for this reason. Merely separating the pellet with the cellular debris from the medium cannot be

interpreted as “purifying the L-amino acid *from the medium*”, as the medium is only obtained as a result of this separation.

Furthermore, Kobayashi teaches away from purifying L-amino acids from any cell culture since the only description of a culture method describes manipulation of the post-centrifugation pellet, which does not contain the objective L-amino acids. The term “purifying” as defined in the specification on page 23, lines 2-7 clearly indicates a manipulative step such as “ion exchange, concentration and crystalline fraction methods...” is performed, which is not described or suggested by the Enzyme Assay of Kobayashi. This represents a further clear error in the interpretation of the claim, as the Examiner has refused to read the claims’ terms in light of the specification. Although it is acknowledged that the purification methods described in the specification at page 23 cannot be imported into the claim, Appellant’s definition in the specification and the term “purifying” as recited in the claims cannot be completely ignored. The Examiner is completely ignoring this definition in the specification, as it clearly indicates that the claim must be interpreted to actually indicate a purification of the amino acid from the medium, not merely separating a medium from a pellet, as is taught by Kobayashi.

The secondary and evidentiary references fail to make up for the deficiencies of Kobayashi. Kaplan is cited for showing that *E.coli* is a well-known L-threonine producer. This fact is not disputed and is well-known in the art. Therefore, this reference adds no further weight to the rejection. Specifically, there would be no motivation or reason to isolate a markedly increased amount of L-threonine from the medium of Kobayashi after purifying the cells after centrifugation. In fact, as shown above, one of ordinary skill in the art would have assumed that the cells and all cellular products would be present in the pellet. Therefore, one of ordinary skill in the art would not have expected a large amount of L-threonine in the medium of Kobayashi, and hence the invention is non-obvious over the cited prior art.

The Georgiou reference allegedly teaches a method of determining the growth phase of *E. coli* by measuring the optical density. To take this measurement, one takes an aliquot during growth. The Examiner asserts it would have been obvious to one of ordinary skill in the art to combine the teachings of Kobayashi and Georgiou to culture the host cell of Kobayashi, and

remove an aliquot of the culture for optical density measurement in order to determine when the cells reached mid-exponential growth phase. The Examiner then states that once the aliquot is taken, one would know to centrifuge the cells and prepare a cell extract of the harvested cells. Kruse is cited as an evidentiary reference to show that *E. coli* is an L-threonine-producing strain. However, Kobayashi fails to teach the recovery or purification of an L-amino acid, nor even any indication that an L-amino acid might be present in the medium following the cultivation and centrifugation of the cultivated cells, and the secondary and evidentiary references fail to make up for this deficiency.

Begot, similar to Georgiou, is cited for showing that it was well-known to determine the growth phase of a bacterial culture medium by monitoring the optical density of the medium. This fact is not disputed, but fails to make up for the deficiencies of Kobayashi. Therefore, this reference adds no further weight to the rejection. Specifically, there would be no motivation or reason to expect a markedly increased amount of L-threonine from the medium after purifying the cells after centrifugation. In fact, as shown above, one of ordinary skill in the art would have assumed that the cells and all cellular products would be present in the pellet. Of course, one might expect a very small amount of L-amino acid to be present in the medium, as it is known that LB medium contains amino acids. However, one of ordinary skill in the art would not have expected a large amount of L-threonine in the medium at this point in the process of the claimed invention, and hence the invention is non-obvious over the cited prior art.

Contrary to the teachings of any of the cited references, the desired product, the L-amino acid, is purified from the supernatant, that is, the medium, after removing solids, including cells, from the medium. This is explicitly stated in the claims, in that step B states that the solids, such as the cells and cellular debris, are removed from the culture medium, and step C states that the L-amino acid is purified from the medium obtained in step B). It is undisputed that this medium is the supernatant obtained after removing the cells and cellular debris.

Simply stated, the cited references fail to teach a method of producing an amino acid, nor is there any suggestion or motivation for adapting any of the alleged teachings for the purpose of producing an amino acid. In the Office Action mailed July 22, 2008, it is stated on page 10 that

“there is no dispute that the objective of the method of the combination of cited references would not be to produce an L-amino acid”. However, the combination of cited references has to teach or suggest the claimed method, and they simply do not. There is no suggestion in any of the references that one of ordinary skill in the art would expect to produce an L-amino acid when conducting the claimed method steps, and the combination particularly does not teach or suggest production of the L-amino acid in a larger amount than if the producing bacteria were not transformed with the claimed DNA.

On page 10-11 it is stated that it has been acknowledged that the host cell taught by Kobayashi is the same as the bacterium which used in step A), and hence it can be assumed that the bacteria will inherently perform the claimed process. However, there is no teaching or suggestion of the explicit method steps, and there is no teaching that the bacteria taught by Kobayashi will perform the claimed method either explicitly or inherently based on the teachings of the cited references. There still must be a teaching of the method, its specific steps, and the claimed outcome, and there is certainly no teaching or suggestion of the claimed method, its specific steps, and certainly not the produced product. There is no teaching or suggestion of a method of producing amino acids according to the claimed method steps, and so the claimed method is simply not obvious over the cited references, either singly or in combination, either inherently or explicitly.

Furthermore, one of ordinary skill must have a reason or motivation to combine the references (*KSR International Co. v. Teleflex Inc. et al.*, No. 04-1350, slip op. at 16 (S.Ct., April 30, 2007)), and there is no commonality in the teachings of these references that would provide a reason for the person of ordinary skill in the art to combine these teachings to arrive at the claimed method. Neither reference has the goal of producing an L-amino acid, nor discusses such production in reference to the methods taught. As neither reference teaches or suggests such a method or even the desire to obtain an L-amino acid, the methods taught by these references fail to render obvious the claimed method. There is no teaching in any of the 4 cited references of step C in the claimed method, nor any suggestion from the various teachings of centrifugation of the various cultures, including the step of removing an aliquot in Georgiou.

Therefore, these references fail to render obvious the claimed invention.

For at least the foregoing reasons, Appellant respectfully submits that the subject matters of Claims 77-84 are not obvious over Kobayashi in view of Kaplan, Georgiou, and Begot, as evidenced by Zakataeva and Kruse, and are therefore not unpatentable under 35 U.S.C. § 103, and therefore Appellant respectfully requests withdrawal of the rejection thereof under 35 U.S.C. § 103.

VIII. Conclusion

For at least the foregoing reasons, Appellant respectfully submits that the subject matters of Claims 77-84, each taken as a whole, are patentable. Accordingly, Appellant respectfully requests reversal of the rejections of Claims 77-84 under section 103(a).

Respectfully submitted,

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APPENDIX A: CLAIMS ON APPEAL

77. (currently amended) A method of producing an L-amino acid comprising
- A) cultivating in a culture medium a bacterium transformed with a DNA that encodes a protein comprising the amino acid sequence of SEQ ID NO: 4,
- B) removing solids including cells from the medium; and
- C) purifying said L-amino acid from the medium obtained in step B),
- wherein said L-amino acid is present in the medium obtained from step B) in a larger amount than that produced if the bacterium of step A) was not transformed with said DNA.
78. (previously presented) The method of claim 77, wherein
- said DNA comprises the nucleotide sequence of nucleotides 187 to 804 of SEQ ID NO: 3.
79. (previously presented) The method of claim 77, wherein the bacterium is further transformed with a second DNA that encodes a protein comprising the amino acid sequence of SEQ ID NO: 2.
80. (previously presented) The method of claim 79, wherein said second DNA comprises the nucleotide sequence of nucleotides 557 to 1171 of SEQ ID NO: 1.
81. (previously presented) The method of claim 77, wherein said L-amino acid is L-threonine.
82. (previously presented) The method of claim 78, wherein said L-amino acid is L-threonine.
83. (previously presented) The method of claim 79, wherein said L-amino acid is L-threonine.
84. (previously presented) The method of claim 80, wherein said L-amino acid is L-threonine.

APPENDIX B: EVIDENCE

None.

APPENDIX C: RELATED PROCEEDINGS

Application 11/106,455 is a divisional of the instant application, and is also currently on appeal before the Board of Patent Appeals and Interferences, the Appeal Brief therein being filed on the same day as this Appeal Brief.